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(57) Abstract

The present invention relates generally to therapeutic molecules. More particularly, the present invention provides therapeutic molecules capable of interacting with Interleukin-13 (IL-13) and to genetic sequences encoding these therapeutic molecules. The therapeutic molecules of the present invention are useful in modulating the action of IL-13 *in vivo*.

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THERAPEUTIC MOLECULES

The present invention relates generally to therapeutic molecules. More particularly, the present invention provides therapeutic molecules capable of interacting with Interleukin-13 (IL-13) and to genetic sequences encoding these therapeutic molecules. The therapeutic molecules of the present invention are useful in modulating the action of IL-13 *in vivo*.

Bibliographic details of the publications referred to by author in this specification are collected at the end of the description. Sequence Identity Numbers (SEQ ID NOs.) for the amino acid sequences referred to in the specification are defined following the bibliography.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

The increasing sophistication of recombinant DNA technology is greatly facilitating research in the medical and allied health fields. A particularly important area of research is in the field of cytokines since these molecules are involved in a host of regulatory mechanisms including roles in immune potentiation, cell differentiation and proliferation and in modulating haemopoietic potentiation activities.

One important cytokine is Interleukin-13 (IL-13) which is produced by activated T-cells and is involved in regulation of the immune response by, for example, inducing immunoglobulin class switching to IgG1 and IgE isotypes and in inhibiting release of inflammatory mediators by macrophages. IL-13 is structurally related to another, functionally similar cytokine, interleukin 4 (IL-4) and both cytokines share common receptor components (Howard and Harada, 1994; McKenzie and Zurawski, 1994; Zurawski and deVries, 1994).

The IL-13 receptor α-chain (IL-13Rα) has recently been cloned (Hilton *et al*, 1996). Analysis of IL-13Rα together with other cloned receptors indicates that IL-13 may first bind IL-13Rα and

then recruit IL-4Rα to form a high affinity receptor. IL-2Rγ does not appear to play a central role in IL-13 receptor function, whereas in the case of IL-4, binding occurs initially with IL-4Rα and this complex may interact with either IL-2Rγ or IL-13Rα to yield a high affinity receptor capable of signal transduction.

The pleiotropic properties of many cytokines such as IL-13 may cause difficulties during treatment regimes. It would be useful to administer IL-13 or a related cytokine to effect a particular response and then to administer a blocking agent to prevent further activity at the localised area. This is also important if the IL-13 administered is capable of inducing an adverse immune response against itself or native IL-13. There are also a range of conditions aggravated by IL-13 such as allergic conditions. The ability to reduce IL-13 action would provide a valuable therapeutic tool in treating these conditions.

In work leading up to the present invention, a high affinity binding protein for IL-13 has been identified in mammalian bodily fluid. The protein is functionally, structurally and antigenically distinct from cloned, soluble IL-13Rα and acts as a potent antagonist of IL-13 action.

Accordingly, one aspect of the present invention provides an isolated proteinaceous molecule or a recombinant or synthetic form thereof capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13Rα.

The proteinaceous molecule may be a peptide, polypeptide or protein and may be naturally or non-naturally glycosylated or unglycosylated. Differential glycosylation patterns may be obtained depending on the host cell which synthesises the proteinaceous molecule. When a recombinant form of the molecule is produced in prokaryotic cells, for example, the molecule would be substantially non-glycosylated. All forms of glycosylation including substantial absence of glycosylation of the subject proteinaceous molecule are encompassed by the present invention.

The proteinaceous molecule and the IL-13 may be derived from the same animal species (ie homologous) or both molecules may be derived for different species (ie heterologous). Animal species contemplated by the present invention include but are not limited to humans, livestock

animals (eg sheep, cattle, horses, donkeys, pigs, goats), laboratory test animals (eg rabbits, guinea pigs, rats, mice), companion animals (eg dogs, cats), and captive wild animals (eg foxes, deer, kangaroos and other marsupials, dingoes). Preferably, the proteinaceous molecule is from humans or murine animals.

The proteinaceous molecule of the present invention may be a naturally occurring molecule in isolated form or may be a functional derivative thereof. A "functional derivative" means that the molecule retains its ability to interact with IL-13 or a related cytokine or a derivative of IL-13. Derivatives contemplated by the present invention include mutants, fragments, parts, portions, truncated forms, fused forms, hybrid forms, homologues and analogues as well as glycosylation variants. All such forms are within the scope of the present invention and are encompassed by the terms "derivative" and "derivatives". The proteinaceous molecule of the present invention is hereinafter referred to as "IL-13 binding protein" (IL-13BP) which includes naturally occurring, recombinant, synthetic and derivative forms thereof.

Reference herein to "isolated" forms of IL-13BP includes reference to a biologically pure preparation of the molecule. Such a purified molecule has undergone at least one purification step from a mixture. Conveniently, a biologically pure preparation is a preparation containing at least about 1%, more particularly at least about 10%, even more particularly at least about 20%, still even more particularly greater than about 30%, eg. 40-50%, 60-70% or above of IL-13BP or its derivative as determined by, for example, weight, binding activity, antagonising ability, immunointeractivity or other convenient means.

Mutants include single or multiple amino acid substitutions, deletions and/or additions to the naturally occurring IL-13BP amino acid sequence.

Hybrid forms include but are not limited to hybrids between IL-13BP and IL-4BP which hybrid being capable of interacting with both IL-13 and IL-4. Accordingly, another aspect of the present invention provides a polypeptide having first and second portions wherein one of said first and second portions is IL-13BP or a functional derivative thereof and the other of said first and second portions is IL-4BP or a functional derivative thereof wherein said polypeptide is

capable of modulating biological processes involving IL-13 and/or IL-4. In one embodiment, there is an amino acid spacer between said first and second portions. The spacer may range from one amino acid to 100 amino acids, more preferably between three amino acids and twenty amino acids and even more preferably between five and fifteen amino acids. The hybrid polypeptide may not necessarily modulate equally IL-13 and IL-4 biological processes but may, for example, be 60-80% effective for IL-13 processes and only 20-50% effective for IL-4 processes or *vice versa*.

Another particularly preferred hybrid comprises IL-13BP or derivative forms thereof and IL-13 receptor α-chain (IL-13Rα) or its derivatives. Such a hybrid may be particularly useful in modulating activities of related molecules such as, but not limited to, IL-13, IL-13BP, IL-13Rα, IL-4, IL-4BP and IL-4 receptor α-chain (IL-4Rα). The IL-13Rα is disclosed in Hilton *et al*, 1996.

Still further hybrids include hybrids between IL-13BPs from different species. For example, a hybrid between all or a functional part of human and murine IL-13BPs.

Analogues of IL-13BP contemplated herein include, but are not limited to, modification to side chains, incorporating unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$.

The guanidine group of arginine residues may be modified by the formation of heterocyclic

condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide.

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 1.

Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition,

peptides can be conformationally constrained by, for example, incorporation of C_α and N_α-methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and the N or C terminus.

These types of modifications may be important to stabilise IL-13BP if administered to an individual or for use as a diagnostic reagent.

The present invention further contemplates chemical analogues of IL-13BP capable of acting as antagonists or agonists of IL-13BP or which can act as functional analogues of IL-13BP which are capable of acting as antagonists of IL-13 activity. Chemical analogues may not necessarily be derived from IL-13BP but may share certain conformational similarities to the molecule as a whole or to its active site(s). Alternatively, chemical analogues may be specifically designed to mimic certain physiochemical properties of IL-13BP. Chemical analogues may be chemically synthesised or may be detected following, for example, natural product screening.

TABLE 1

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α-aminobutyric acid	Abu	L-N-methylalanine	Nmala
α-amino-α-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
aminocyclopropane-carboxylate	Cpro	L-N-methylasparagine	Nmasn
		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-carboxylate	Norb	L-N-methylglutamine	Nmgln
		L-N-methylglutamic acid	Nmglu
cyclohexylalanine		Chexa L-N-methylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisolleucine	Nmile
D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva

D-tyrosine	Dtyr	α-methyl-aminoisobutyrate	Maib
D-valine	Dval	α-methyl-γ-aminobutyrate	Mgabu
D-α-methylalanine	Dmala	α-methylcyclohexylalanine	Mchexa
D-α-methylarginine	Dmarg	α-methylcylcopentylalanine	Mcpen
D-α-methylasparagine	Dmasn	α-methyl-α-napthylalanine	Manap
D-α-methylaspartate	Dmasp	α-methylpenicillamine	Mpen
D-α-methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
D-α-methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
D-α-methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
D-α-methylisoleucine	Dmile	N-amino-α-methylbutyrate	Nmaabu
D-α-methylleucine	Dmleu	α-napthylalanine	Anap
D-α-methyllysine	Dmlys	N-benzylglycine	Nphe
D-α-methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
D-α-methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
D-α-methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
D-α-methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
D-α-methylserine	Dmser	N-cyclobutylglycine	Ncbut
D-α-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
D-α-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
D-α-methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
D-α-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
D-N-methylhistidine	Dnmhis	N-(hydroxyethyl))glycine	Nser
D-N-methylisoleucine	Dnmile	N-(imidazolylethyl))glycine	Nhis
D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp

D-N-methyllysine	Dnmlys	N-methyl-γ-aminobutyrate	Nmgabu
N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
D-N-methyltyrosine	Dnmtyr	N-methyla-napthylalanine	Nmanap
D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
γ-aminobutyric acid	Gabu	N-(*p*-hydroxyphenyl)glycine	Nhtyr
L-*t*-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
L-ethylglycine	Etg	penicillamine	Pen
L-homophenylalanine	Hphe	L-α-methylalanine	Mala
L-α-methylarginine	Marg	L-α-methylasparagine	Masn
L-α-methylaspartate	Masp	L-α-methyl-*t*-butylglycine	Mtbug
L-α-methylcysteine	Mcys	L-methylethylglycine	Metg
L-α-methylglutamine	Mgln	L-α-methylglutamate	Mglu
L-α-methylhistidine	Mhis	L-α-methylhomophenylalanine	Mhphe
L-α-methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
L-α-methylleucine	Mleu	L-α-methyllysine	Mlys
L-α-methylmethionine	Mmet	L-α-methylnorleucine	Mnle
L-α-methylnorvaline	Mnva	L-α-methylornithine	Morn
L-α-methylphenylalanine	Mphe	L-α-methylproline	Mpro
L-α-methylserine	Mser	L-α-methylthreonine	Mthr
L-α-methyltryptophan	Mtrp	L-α-methyltyrosine	Mtyr

L-α-methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane	Nmbc		

In a particularly preferred embodiment, the interaction between IL-13BP and IL-13 results in antagonism of IL-13 activity. The antagonism may be from mild to substantial in relation to at least one property attributable to IL-13. For example, the antagonism may result in about 1-10% reduction or about 10-30% reduction or about 30-50% reduction or about 50-70% or greater (eg >90%) relative to at least one property attributable to IL-13 or a related cytokine. In a particularly preferred embodiment, IL-13BP binds to IL-13 with a greater than 50-fold higher affinity compared to IL-13Rα.

Another aspect of the present invention contemplates a method for purifying IL-13BP or its derivatives or hybrid forms from a biological sample including body fluid or cell culture medium, said method comprising contacting said biological sample with immobilised IL-13 (or an IL-13/IL-4 hybrid) or a binding derivative thereof for a time and under conditions sufficient for a complex to form between said IL-13 (or IL-13/IL-4) and its binding protein, eluting said IL-13BP (or IL-13/IL-4) from the immobilised IL-13 (or IL-13/IL-4) and collecting said eluted IL-13BP.

Preferably, the eluate is subjected to further purification on an HPLC or equivalent chromatography.

Preferably, the HPLC or equivalent chromatographic purified samples are further purified or analysed on SDS-PAGE.

The IL-13BP is antigenically, structurally and functionally distinct from IL-13Rα. IL-13BP is isolatable from biological fluid such as from urine or other excretable fluid, circulatory fluid

such as from serum, whole blood, plasma or lymph fluid or respiratory fluid such as sputum, nasal secretion and saliva. The biological fluid may also comprise medium conditioned by human or animals cells, cell lines, organs and/or tissues. Preferably, the IL-13BP is isolatable from urine or serum.

Native soluble IL-13BP has an apparent molecular mass of approximately 40,000 to 60,000 daltons and more preferably about 55,000 ±5,000 daltons. Conveniently, the molecule weight may be determined by SDS-PAGE.

In a particularly preferred embodiment of the present invention, there is provided an isolated proteinaceous molecule comprising the following properties:

(i) has a molecular weight in its native soluble form of from about 40,000 to about 60,000 daltons;

(ii) is isolatable in its native soluble form from urine or serum;

(iii) is capable in its native soluble form of binding to IL-13 with greater affinity than IL-13Rα;

(iv) is antigenically and structurally distinct from IL-13Rα; and

(v) migrates as a single band on SDS-PAGE;

or a derivative of said proteinaceous molecule.

Preferably, the proteinaceous molecule is an antagonist of at least one property attributable to IL-13.

Another aspect of the present invention provides an isolated IL-13BP comprising the amino acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.

Still another aspect of the present invention provides an isolated IL-13BP comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.

Even yet another aspect of the present invention provides an isolated IL-13BP comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.

In yet a further aspect of the present invention provides an isolated IL-13BP comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

Yet another aspect of the present invention provides an isolated IL-13BP having an amino acid sequence set forth in one of SEQ ID NO:6 or 7 or 8 (N-terminal sequence) or SEQ ID NO:10 or 11 or 12 (C-terminal sequence) or comprises at least about 50% similarity and more preferably at least about 60%, still more preferably at least about 75-80% similarity to at least one of SEQ ID NO:6 or 7 or 8 or 10 or 11 or 12.

Reference herein to N- or C-terminal sequences include reference to a region at the N- or C-terminal portion of the molecule. It does not, for example, imply any limitation as to including the initiating methione although such a methione may be included in said N-terminal sequence.

In still yet another aspect of the present invention, there is provided an isolated human IL-13BP having the amino acid sequence corresponding to SEQ ID NO:20 or a sequence having at least about 50% similarity thereto.

Another aspect of the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides which encodes or is complementary to a sequence which encodes a proteinaceous molecule capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13Rα.

More particularly, the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides which encodes or is complementary to a sequence which encodes a proteinaceous molecule comprising the following properties:

(i) has a molecular mass in its native soluble form of from about 40,000 to about

60,000 daltons;

(ii) is isolatable in its native soluble form from urine or serum;

(iii) is capable in its native soluble form of binding to IL-13 with greater affinity than IL-13Rα;

(iv) is antigenically and structurally distinct from IL-13Rα; and

(v) migrates as a single band on SDS-PAGE;

or a derivative of said proteinaceous molecule.

Sub paragraph (i) above is not intended to limit the molecule of the present invention to a soluble form of from 40,000 to 60,000 daltons but rather the native soluble form of the molecule would have these characteristics.

Preferably, the proteinaceous molecule is an antagonist of at least one property attributable to IL-13.

Preferably, the nucleic acid molecule is capable of hybridising with low stringency conditions to one or both of 5' ATGGCTTTCGTTTGCTTGGCTATC3' [SEQ ID NO:2] and/or 5'CAACATTCGCAAGAAAAATTCAGTTTATT3' [SEQ ID NO:3] or complementary forms thereof. Preferably, the nucleic acid molecule encodes a proteinaceous molecule comprising the amino acid sequence set forth in SEQ ID NO:1 or 13 or 21 or 22. Alternatively or in addition, a preferred nucleic acid molecule encodes an N-terminal amino acid sequence as set forth in one of SEQ ID NO:6 or 7 or 8 or a C-terminal amino acid sequence as set forth in SEQ ID NO:10 or 11 or 12.

In a particularly preferred embodiment, the amino acid sequence is as set forth in SEQ ID NO:19.

Even more preferably the nucleic acid molecule comprises the nucleotide sequence set forth in SEQ ID NO:5 and/or SEQ ID NO:9 and/or 19 or a nucleic acid molecule capable of hybridizing under low stringency conditions at 42°C and/or is a nucleic acid molecule having at least about 50% nucleotide sequence similarity thereto.

Preferred similarities include at least about 60%, at least about 75% and at least about 85-90% to all or preferably to at least 20 contiguous base pairs of the nucleotide sequences set forth in SEQ ID NO:5 and/or SEQ ID NO:9 and/or SEQ ID NO:19.

Reference herein to a low stringency at 42°C includes and encompasses from at least about 1% v/v to at least about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions.

The nucleic acid molecule may be genomic DNA in isolated form or cDNA or mRNA or hybrid forms thereof. The nucleotide sequence may correspond to the native genomic sequence or the cDNA sequence or may comprise single or multiple nucleotide substitutions, deletions and/or additions.

The nucleic acid molecules are generally in isolated form but may also be integrated into or ligated to or otherwise fused or associated with other genetic molecules such as vector molecules and in particular expression vector molecules. Vectors and expression vectors are generally capable of replication and, if applicable, expression in one or both of a prokaryotic cell or a eukaryotic cell. Preferably, prokaryotic cells include *E. coli, Bacillus sp* and *Pseudomonas sp.* Preferred eukaryotic cells include yeast, fungal, mammalian and insect cells.

Accordingly, another aspect of the present invention contemplates a genetic construct comprising a vector portion and a mammalian IL-13BP gene portion or a derivative thereof, which IL-13BP gene portion encodes an IL-13BP peptide, polypeptide or protein or a functional or immunologically interactive derivative thereof capable of binding to IL-13.

Preferably, the IL-13BP gene portion of the genetic construct is operably linked to a promoter, such as on the vector, such that said promoter is capable of directing expression of said IL-13BP gene portion in an appropriate cell.

In addition, the IL-13BP gene portion of the genetic construct may comprise all or part of the gene fused to another genetic sequence such as a nucleotide sequence encoding glutathione-S-transferase or part thereof.

The IL-13BP of the present invention or its derivatives are contemplated to be useful, *inter alia*, in the antagonism of at least one IL-13 activity. This may be important for IL-13 mediated conditions such as certain allergic conditions such as asthma or to inactivate locally administered IL-13 after IL-13 treatment.

Accordingly, another aspect of the present invention contemplates a method of treatment comprising administering to a patient an IL-13 antagonising effective amount of an IL-13BP or its derivative for a time and under conditions sufficient to antagonise at least one property of IL-13. For example, IL-13 may have the effect of increasing the level of receptors for rhinoviruses. Antagonising IL-13 would have the effect of reducing adverse rhinovirus interaction such as interaction leading to asthma.

In one embodiment, the treatment is for an allergic response or allergic reaction.

In an alternative embodiment, there may be circumstances where IL-13BP complexes with IL-13 can, in fact, enhance cytokine mediated processes. Accordingly, this embodiment is encompassed by the present invention.

The present invention contemplates, therefore, a pharmaceutical composition comprising IL-13BP or a derivative thereof or a modulator of IL-13BP gene expression or IL-13BP activity and one or more pharmaceutically acceptable carriers and/or diluents. These components are referred to as the "active ingredients".

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful

compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 μg and 2000 mg of active compound. Alternative dosage amounts include from about 1 μg to about 1000 mg, from about 10 μg to above 800 mg and from about 20 μg to about 500 mg.

The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter. A binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such a sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

The present invention also extends to forms suitable for topical application such as creams, lotions and gels.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from 0.5 μg to about 2000 mg. Expressed in proportions, the active compound is generally present in from about 0.5 μg to about 2000 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

The effective amount of the active ingredient may be as defined above but must be in an amount effective to have the desired effect. Conveniently, this may be expressed as an amount per kilogram (kg) body weight and includes from about 10 ng to about 2000 mg/kg body weight, about 100 ng to about 1000 ng/kg body weight and about 1-10 μg to above 500 ng/kg body weight.

The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating IL-13BP gene expression or IL-13BP activity. The vector may, for example, be a viral vector.

Still another aspect of the present invention is directed to antibodies to IL-13BP and its

derivatives. These antibodies may be directed to soluble IL-13BP or cell surface bound IL-13BP. Antibodies and in particular antibodies directed to the cell surface bound IL-13BP may function as antagonists. The antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to IL-13BP or may be specifically raised to IL-13BP or derivatives thereof. The antibodies may also be anti-idiotypic antibodies to the active site of IL-13BP. IL-13BP or its derivatives may first need to be associated with a carrier molecule in order to generate the antibodies.

The subject antibodies and/or IL-13BP or its derivatives of the present invention are particularly useful as therapeutic or diagnostic agents.

For example, IL-13BP and its derivatives can be used to screen for naturally occurring antibodies to IL-13BP. These may occur, for example in some autoimmune diseases. Alternatively, specific antibodies can be used to screen for IL-13BP. Techniques for such assays are well known in the art and include, for example, sandwich assays and ELISA. Knowledge of IL-13BP levels may be important for diagnosis of certain disease conditions associated with IL-13. The IL-13BP may also be used to assay for IL-13 directly or via antibodies.

Antibodies to IL-13BP of the present invention may be monoclonal or polyclonal. Alternatively, fragments of antibodies may be used such as Fab fragments. Furthermore, the present invention extends to recombinant and synthetic antibodies and to antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies. The antibodies of this aspect of the present invention are particularly useful for immunotherapy and may also be used as a diagnostic tool for assessing, for example, apoptosis or monitoring the program of a therapeutic regimin.

For example, specific antibodies can be used to screen for IL-13BP proteins. The latter would be important, for example, as a means for screening for levels of IL-13BP in a cell extract or other biological fluid or purifying IL-13BP made by recombinant means from culture supernatant fluid. Techniques for the assays contemplated herein are known in the art and

include, for example, sandwich assays and ELISA.

It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies discussed above. Both the first and second antibodies may be used in detection assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of IL-13BP.

Both polyclonal and monoclonal antibodies are obtainable by immunization with the enzyme or protein and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively easily prepared by injection of a suitable laboratory animal with an effective amount of IL-13BP, or antigenic parts thereof, collecting serum from the animal, and isolating specific sera by any of the known immunoadsorbent techniques. Although antibodies produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation can be done by techniques which are well known to those who are skilled in the art.

Another aspect of the present invention contemplates a method for detecting IL-13BP in a biological sample from a subject said method comprising contacting said biological sample with an antibody specific for IL-13BP or its derivatives or homologues for a time and under conditions sufficient for an antibody-IL-13BP complex to form, and then detecting said complex.

The presence of IL-13BP may be detected in a number of ways such as by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by

reference to US Patent Nos. 4,016,043, 4, 424,279 and 4,018,653. These, of course, include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labelled antibody to a target.

Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labelled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labelled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In accordance with the present invention the sample is one which might contain IL-13BP including cell extract, tissue biopsy or possibly serum, saliva, mucosal secretions, lymph, tissue fluid and respiratory fluid. The sample is, therefore, generally a biological sample comprising biological fluid but also extends to fermentation fluid and supernatant fluid such as from a cell culture.

In the typical forward sandwich assay, a first antibody having specificity for the IL-13BP or antigenic parts thereof, is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally

consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or overnight if more convenient) and under suitable conditions (from about room temperature to about 40°C, eg. 25-37°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

Another particularly useful alternative is to use IL-13 or a hybrid form thereof (eg. IL-13/IL-4) immobilised to a solid support to bind to IL-13BP and then to use an antibody to IL-13BP to detect binding to the immobilised IL-13. The antibody may be labelled or an anti-immunoglobulin or an anti-immunoglobulin antibody labelled with a reporter molecule could be used.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody,

generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable colour change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labelled antibody is added to the first antibody hapten complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample. "Reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescence and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

The present invention also contemplates genetic assays such as involving PCR analysis to detect IL-13BP gene or its derivatives. Alternative methods or methods used in conjunction include direct nucleotide sequencing or mutation scanning such as single stranded conformation

polymorphoms analysis (SSCP) as specific oligonucleotide hybridisation, as methods such as direct protein truncation tests.

The present invention also extends to immobilised IL-13 or derivatives thereof useful in the purification of IL-13BP. Biological fluid is contacted with the immobilised IL-13 for a time and under conditions for a IL-13-IL-13BP complex to form. The IL-13BP is then eluted from the immobilised IL-13 and subjected to further purification steps.

A further aspect of the present invention contemplates an isolated polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or 13 or 21 or 22 or an amino acid sequence set forth in SEQ ID NO:6 or 7 or 8 or 10 or 11 or 12 or 20 or having at least about 30% similarity to any one or more thereof. Preferred percentage similarities include at least about 40-50%, more preferably at least about 60-70%, and even more preferably at least about 80-90% or above. The polypeptide of this aspect of the present invention preferably has IL-13BP properties or is a derivative thereof or is a hybrid form thereof.

The present invention further contemplates knockout animals such as mice or other murine species for the IL-13BP gene including homozygous and heterozygous knockout animals. Such animals provide a particularly useful live *in vivo* model for studying the effects of IL-13BP as well as screening for agents capable of acting as agonists or antagonists of IL-13BP.

According to this embodiment there is provided a transgenic animal comprising a mutation in at least one allele of the gene encoding IL-13BP. Additionally, the present invention provides a transgenic animal comprising a mutation in two alleles of the gene encoding IL-13BP. Preferably, the transgenic animal is a murine animal such as a mouse or rat.

The present invention is further described by the following non-limiting Figures and Examples.

In the Figures:

Figure 1 is a graphical representation of IL-13 binding to IL-13BP in mouse urine and serum

and soluble IL-13Rα by gel filtration chromatography. The gel filtration column was equilibrated and run in TBS at 0.5 ml/min as described in the Examples. Panel A: ^{125}I-IL-13 alone (20,000 cpm); Panels C, E and G: ^{125}I-IL-13 (20,000 cpm) + 100 μl DBA/2J mouse serum or in the presence of either 1 μg/ml unlabelled IL-13 or IL-4, respectively; Panel B: ^{125}I-IL-13 alone (50,000 cpm); Panels D, F and H: ^{125}I-IL-13 (50,000 cpm) + 100 μl NodL$^+$/Jax mouse urine or in the presence of either 1 μg/ml unlabelled IL-13 or IL-4, respectively.

Figure 2 is a graphical representation of ^{125}I-IL-13 binding to soluble IL-13Rα and IL-13BP by gel filtration chromatography. Panel A: ^{125}I-IL-13 (50,000 cm) + 10 μg/ml soluble IL-13Rα; Panel B: ^{125}I-IL-13 (50,000 cpm) + 10 μg/ml soluble IL-13Rα + 0.5 μg/ml soluble IL-4Rα.

Figure 3 is a graphical representation showing a comparison of the ability of IL-13BP and soluble IL-13Rα to inhibit the binding of IL-13 to its cell surface receptor. 10^5 cpm of ^{125}I-IL-13 and ^{125}I-GM-CSF were incubated for 40 min at 4°C with indicated dilution of partially purified urinary IL-13BP (A) or with the indicated concentration of soluble IL-13Rα (B). The labelled ligand and the soluble IL-13Rα or IL-13BP were then added to 50 μl of medium containing $1.5x10^6$ peritoneal cells from a GM-CSF transgenic mouse. Incubation was continued for a further 2 hr at 4°C before cell-associated and free ^{125}I-IL-13 or ^{125}I-GM-CSF were separated by centrifugation of cells through 200 μl of foetal calf serum. The resulting cell pellets and supernatants were then counted in a γ-counter and specific binding was calculated as the difference between the ^{125}I-ligand bound in the absence and presence of the unlabelled competitor, in turn this was expressed as a percentage of that observed in the absence of either soluble IL-13Rα or IL-13BP(●). As a control both soluble IL-13Rα and IL-13BP showed no inhibition of ^{125}I-GM-CSF binding (O) to peritoneal cells.

The following single and three letter abbreviations are used for amino acid residues:

Amino Acid	Three-letter Abbreviation	One-letter Symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any residue	Xaa	X

SUMMARY OF SEQ ID NOs.

SEQUENCE	SEQ ID NOs:
Amino acid sequence of N-terminal IL-13BP [generic]	1
Oligonucleotide capable of hybridising to human IL-13BP DNA (or complementary form thereof)	2
Oligonucleotide capable of hybridising to human IL-13BP DNA (or complementary form thereof)	3
FLAG peptide	4
Nucleotide sequence of N-terminal region of human IL-13BP (R52795)	5
Amino acid sequence of N-terminal region of human IL-13 BP	6
Amino acid sequence of N-terminal region of human IL-13 BP	7
Amino acid sequence of N-terminal region of human IL-13 BP	8
Nucleotide sequence of C-terminal region of human IL-13BP (R52796)	9
Amino acid sequence of C-terminal region of human IL-13BP	10
Amino acid sequence of C-terminal region of human IL-13BP	11
Amino acid sequence of C-terminal region of human IL-13BP	12
Amino acid sequence of N-terminal region of IL-13BP [partially generic]	13
Putative signal sequence in human IL-13BP	14
Oligonucleotide primers for PCR cloning of human IL-13BP	15
Oligonucleotide primers for PCR cloning of human IL-13BP	16
Nucleotide sequence of construct containing human IL-13BP cDNA	17
Amino acid sequence of SEQ ID NO:17	18
Nucleotide sequence of human IL-13BP	19
Amino acid sequence of human IL-13BP	20
Amino acid sequence of N-terminal IL-13BP [murine]	21
Amino acid sequence of N-terminal IL-13BP [human]	22

EXAMPLE 1
REAGENTS

Recombinant murine IL-13 was produced as a FLAG-tagged protein in *Pichia pastoris*. Recombinant mouse IL-4 were purchased from R & D Systems. Recombinant soluble mouse IL-4Rα was from Genzyme. N-Glycosidase F and protease V8 (sequencing grade) were obtained from Boehringer. BS^3 (Bis (Sulfosuccimidyl) suberate) was from Pierce. FLAG peptide (DYKDDDDK [SEQ ID NO:4]) and anti-FLAG M2 affinity gel were purchased from Scientific Imaging Systems. Soluble mouse IL-13 receptor α-chain (IL-13Rα) which was N-terminally-tagged with a FLAG epitope was expressed in CHO cells and purified from CHO cell-conditioned medium on an anti-FLAG M2 affinity column by affinity elution with free FLAG peptide. Anti-IL-13Rα polyclonal antiserum was prepared by injecting purified soluble IL-13Rα into rabbits which were bled after 3 months.

EXAMPLE 2
GEL FILTRATION CHROMATOGRAPHY

Aliquots of samples were incubated with ^{125}I-IL-13 in the presence or absence of a competitor for at least 30 min at 4°C in a final volume of 200 μl. The mixtures were applied to a Superdex 200 10/30 column (Pharmacia), equilibrated in 20 mM Tris-buffered saline, pH 7.0, containing 0.02% (v/v) Tween-20 and 0.02% (w/v) sodium azide. Samples were eluted with TBS at a flow rate of 0.5 ml/min, and 0.5-ml fractions were collected and counted in a γ-counter.

EXAMPLE 3
CROSSLINKING ASSAY

Aliquots of 10- to 20-fold concentrated mouse urine were incubated with ^{125}IL-13 or ^{125}I-IL-4 in the presence or absence of a competitor in a final volume of 20 μl for at least 30 min at 40°C. Then 5 μl of a 12 mM BS^3 solution in PBS containing 0.02% (v/v) Tween-20 was added and the mixtures were incubated for 30 min at 4°C. Samples were mixed with 8 μl of four-time concentrated SDS sample buffer and analysed by 13% (w/v) SDS/PAGE under non-reducing

conditions. The gels were dried and visualised by either autoradiography or PhosphorImager.

EXAMPLE 4

^{125}I-IL-13 SATURATION BINDING ASSAY

Binding of ^{125}I-IL-13 to COS-7 cells expressing IL-13Rα was performed as previously described (Hilton *et al*, 1996). Binding of ^{125}I-IL-13 to soluble proteins in mouse serum and urine was determined by a gel filtration-based assay using Sephadex G-50 minicolumns (Nick column, Pharmacia) to separate free from bound ligand. Briefly, 50 μl of serum or 90 μl of urine per tube was incubated for at least 30 min at 4°C with different amounts of ^{125}I-IL-13 in a final volume of 100 μl. The mixtures were applied to 1.2 ml Sephadex G-50 columns previously washed with 20 mM Tris-buffered saline, pH 7.0, containing 0.02% (v/v) Tween-20 and 0.02% (w/v) sodium azide. After washing the columns with 350 μl of column buffer, bound ^{125}I-IL-13 was eluted with 300 μl of buffer, whereas free ^{125}I-IL-13 was eluted with 600 μl of buffer. Specific binding was calculated by subtracting the cpm bound in the presence of 0.5 μg/ml unlabelled IL-13 (nonspecific binding) from the cpm bound in its absence (total binding). Scatchard analyses of saturation binding isotherms were performed using the curve-fitting program Ligand (McPherson, 1985; Munson and Rodbard, 1980).

EXAMPLE 5

DEGLYCOSYLATION AND V8 DIGESTION

After SDS/PAGE, the gel, which contained ^{125}I-IL-13 crosslinked to either IL-13BP from mouse urine or purified soluble IL-13Rα, was sliced according to pre-stained molecular weight markers. The gel pieces were added with 10 μl of Milli-Q water and 15 μl of 0.1 M sodium phosphate buffer (pH 7.0) containing 10 mM EDTA, 0.1% (w/v) SDS, 0.01% (v/v) β-mercaptoethanol and minced into small pieces with a pair of tweezers. Then 15 μl of 0.1 M sodium phosphate buffer (pH 7.0) containing 10 mM EDTA was added to the minced-gel mixtures. After 1 hr incubation at 37°C, the mixtures were heated for 1 min at 95°C, cooled down, 4 μl of 10% v/v β-octylglucoside added, and treated with N-glycosidase F (0.5 unit in 2.5 μl) overnight at 37°C to complete the deglycosylation. The deglycosylated sample

mixtures were then centrifuged and the gel pieces removed. The recovered liquid portions of the deglycosylated samples were further digested with protease V8 at concentrations ranging from 5 to 60 μg/ml for 3 hr at 37°C. The samples were analysed by a 15% (w/v) SDS/PAGE under non-reducing conditions.

EXAMPLE 6
IMMUNOPRECIPATATION

Aliquots of 10-fold concentrated mouse urine or 3 μg/ml purified soluble IL-13Rα were incubated with ^{125}I-IL-13 in the presence or absence of 0.5 μg/ml unlabelled IL-13 and crosslinking was then performed as described above. The crosslinking reaction was terminated by adding 1M Tris-HCl buffer (pH 7.5) to a final concentration of 40 mM. The crosslinked samples were then mixed with 1:50 diluted control rabbit serum or anti-IL-13Rα antiserum which had been pre-incubated with or without FLAG peptide at a concentration of 100 μg/ml in order to eliminate false immunoreaction with potential anti-FLAG antibody in the anti-IL-13Rα polyclonal antiserum. After 30-min incubation at 4°C, the mixtures were added with 40 μl of 50% (v/v) protein G-Sepharose gel slurry (Pharmacia) and incubated for 30 min at 4°C. The samples were centrifuged and the protein G-Sepharose beads were washed 3 x 0.5 ml PBS, mixed with 40 μl of two-time concentrated SDS sample buffer and heated for 2 min at 95°C. The supernatants were then analysed by a 13% (w/v) SDS/PAGE under non-reducing conditions.

EXAMPLE 7
PRODUCTION AND PREPARATION OF mIL-13 AFFINITY SUPPORT

Mouse IL-13 was produced as a N-terminally FLAG-tagged fusion protein in *Pichia pastoris* and applied to an anti-FLAG antibody (M2) affinity column, non-binding proteins were washed from the column with phosphate-buffered saline containing 0.02% (v/v) Tween 20 after which the proteins that bound to the column, including the FLAG-tagged IL-13, were eluted with free FLAG peptide. The IL-13 was further purified by RP-HPLC. To prepare mIL-13 affinity support, the FLAG-tagged mIL-13 was first coupled to anti-FLAG antibody M2 affinity beads

(Kodak) and then covalently linked to the M2 beads by the chemical cross-linker, BS^3 (Pierce).

EXAMPLE 8

PURIFICATION OF mIL-13 BINDING PROTEIN

100 ml of concentrated mouse urine was incubated with mIL-13 affinity beads for 2 hr at room temperature. After removing unbound protein by centrifugation, the mIL-13 affinity beads were washed extensively with phosphate-buffered saline, pH 7.0, containing 0.02% (v/v) Tween-20 and 0.02% (w/v) sodium azide. The bound protein was eluted with Actisep elution medium (Sterogenes Bioseparations). The eluates containing the active IL-13 binding protein was loaded onto a C8 reversed-phase HPLC column to achieve further purification. Aliquots of fractions eluted from the RP-HPLC column was further analysed by SDS-PAGE, after which the gel was silver stained. Fractions were also analysed for their ability to bind to ^{125}I-IL-13 using the cross-linking protocol described above.

EXAMPLE 9

IDENTIFICATION OF IL-13BP

Given the expression of transmembrane and secreted forms of many members of the haemopoietin receptor family from alternatively spliced transcripts, the inventors sought to determine if this was the case for the IL-13Rα.

Using an analytical gel filtration-based assay, mouse serum and urine were examined for the presence of an IL-13 binding protein (referred to hereon as "IL-13BP"). Analytical gel filtration chromatography of ^{125}I-IL-13 alone resulted in elution of radioactivity in fractions 35 to 39 (Figures 1A and 1B). Prior addition of mouse serum or mouse urine to the ^{125}I-IL-13 resulted in the presence of an addition peak of ^{125}I-IL-13 eluting earlier in fractions 27 to 30 (Figure 1C and 1D), this higher molecular weight peak was competed for by the addition of an excess of unlabelled IL-13 but not unlabelled IL-4, demonstrating that the interaction with IL-13BP was specific (Figures 1E and 1F).

In contrast to crude mouse urine, purified soluble IL-13Rα, appeared unable to bind IL-13 as assessed by gel filtration chromatography (Figure 2A). The very low affinity of IL-13 for the IL-13Rα (Hilton *et al*, 1996) suggested that the serum and urine IL-13BP were either distinct from the IL-13Rα or contained other components in addition to IL-13Rα. One candidate for a protein capable of interaction with IL-13Rα to generate a high affinity IL-3 receptor is the IL-4Rα. The presence of IL-4Rα in urine and serum has been described in a number of previous studies. This result was confirmed by gel filtration chromatography, however, despite the presence of an IL-4 binding protein in urine and serum, addition of purified IL-4Rα to purified IL-13Rα did not recapitulate the properties of the IL-13BP found in serum and urine as assessed by gel filtration chromatography (Figure 2B).

In order to assess the size of the IL-13BP and its relationship to the IL-4 binding protein, mouse urine was fractionated on a preparative gel filtration column. Aliquots from each fraction were then mixed with ^{125}I-IL-13 or ^{125}I-IL-4 in the presence or absence of an excess of unlabelled IL-4 or IL-13 and subject to cross-linking using the bi-functional reagent dimethyl succinimydyl suberate (DSS). The products of the cross-linking reaction were then resolved by SDS-polyacrylamide electrophoresis and visualised by autoradiography. Cross-linking of ^{125}I-IL-13 to unfractionated mouse urine revealed the presence of a major band that electrophoresed with an apparent molecular mass of approximately 70,000 daltons. Given ^{125}I-IL-13 electrophoreses with an apparent molecular mass of 15,000 daltons, this would suggest the IL-13BP has an apparent molecular mass of 55,000 daltons. Cross-linking to the IL-13BP was specific since it was in competition with unlabelled IL-13 but not IL-4. The Mr 55,000 dalton IL-13BP eluted from the gel filtration column in fractions 27 to 29, consistent with its molecular weight estimated from the cross-linking experiment. Additional non-specific lower molecular radioactive products were also observed in the cross-linking studies with ^{125}I-IL-13. One of these eluted from the gel filtration column in fractions 29 and 30, after the Mr 55,000 dalton IL-13BP, but in a similar position to an IL-4 binding protein. Cross-linking of ^{125}I-IL-4 to the IL-4 binding protein resulted in a species migrating with an apparent molecular weight of approximately 55,000 daltons, suggesting the binding protein itself had a molecular mass of 35,000 daltons.

The specificity of the Mr 55,000 dalton IL-13BP to purified receptor components was examined further using cross-linking. Although binding of ^{125}I-IL-13 to purified IL-13Rα was not detected by gel filtration chromatography, an interaction was observed using cross-linking. Consistent with previous studies (Hilton *et al*, 1996), this interaction was competed for by unlabelled IL-13 but not unlabelled IL-4. Cross-linking studies were performed using ^{125}I-IL-13 and purified IL-4Rα and a product with an apparent molecular weight 55,000 was observed. Surprisingly, cross-linking of ^{125}I-IL-13 to IL-4Rα was in competition with unlabelled IL-4 but not IL-13. Combining purified IL-13Rα and IL-4Rα with ^{125}I-IL-13 resulted in the generation of species similar in molecular weight and specificity to reactions containing each receptor alone. No higher molecular weight complexes were observed suggesting that formation of ternary IL-13/IL-13Rα/IL-4Rα complexes or their capture with the cross-linker occurred inefficiently in solution, even at high concentrations of each component. Consistent with the initial experiment, crude mouse urine contained a major Mr 55,000 dalton IL-13BP. Cross-linking of ^{125}I-IL-13 to this species was in competition with unlabelled IL-13 but not unlabelled IL-4. The lower molecular species observed in our initial experiment, was again observed. As before, cross-linking of ^{125}I-IL-13 to this protein was not in competition with unlabelled IL-13; however, like cross-linking ^{125}I-IL-13 to purified IL-4Rα, cross-linking to this protein was competed for by IL-4. Although the addition of purified IL-4Rα to purified IL-13Rα did not alter the pattern of cross-linking observed to either component alone, the inventors sought to determine whether purified IL-4Rα could interact with partially purified 50,000 Mr IL-13BP from mouse urine. As with the purified receptor components, no effect of adding IL-4Rα was observed.

While interaction between IL-13 and both purified soluble IL-13Rα and the Mr 55,000 dalton IL-13BP was demonstratable by cross-linking, only the interaction with the IL-13BP was detectable using analytical gel filtration chromatography. These results suggested that the affinity of IL-13 for the IL-13BP was higher than for soluble IL-13Rα. In order to test this formally, saturation binding experiments were performed. Scatchard transformations reveal that, consistent with previous studies (Hilton *et al*, 1996), the affinity of IL-13 for the IL-13Rα expressed by CHO cells was approximately 10 nM. However, the affinity of IL-13 for serum and urinary IL-13BP was 100 to 300-fold higher, ranging from 20 to 90 pM. The difference

in affinity was confirmed in cross-linking experiments in which ^{125}I-IL-13 was mixed with increasing concentrations of unlabelled IL-13 prior to cross-linking to soluble IL-13Rα or urinary IL-13BP. Densitometric analysis of these data demonstrates that half-maximal inhibition of binding to soluble IL-13Rα occurred with approximately 100 ng/ml IL-13, a 40-fold higher concentration than required to inhibit fifty percent of the cross-linking to the Mr 55,000 dalton urinary IL-13BP.

The structural relationship between soluble IL-13Rα and the Mr 55,000 dalton urinary IL-13BP was examined by cross-linking ^{125}I-IL-13 to both proteins and isolating the resultant complexes. Each complex was then subject to exhaustive deglycosylation using N-glycosidase F and digestion with various concentrations of V8 protease. The products of these treatments were then resolved by SDS-polyacrylamide gel electrophoresis. The untreated and deglycosylated complex of IL-13 and the soluble ^{125}I-IL-13 appeared larger than the corresponding complex with the urinary IL-13BP. In addition, the products of V8 proteolysis of the two complexes were clearly different, emphasising the structural difference between the IL-13Rα and the Mr 55,000 dalton urinary IL-13BP.

A polyclonal antisera to the IL-13Rα was raised in rabbits. This antisera was capable of immunoprecipitating the cross-linked product of ^{125}I-IL-13 with IL-13Rα, while no immunoprecipitation was observed with a pre-immune rabbit sera. Immunoprecipitation of the complex was not inhibited by the FLAG peptide but was inhibited by an excess of IL-13Rα. In contrast to the IL-13R complex, the complex between the Mr 55,000 dalton urinary IL-13BP and ^{125}I-IL-13 was not recognised by the rabbit antisera to IL-13Rα suggesting that these proteins are antigenically, as well as structurally and functionally distinct.

Soluble receptors for a variety of cytokines have been described. In some cases these act to augment a biological response, while in other situations they may inhibit the biological effect. In order to determine whether the purified soluble IL-13Rα or the urinary IL-13BP could influence an IL-13 response, the inventors examined their effects on peritoneal macrophages. Figure 3 demonstrates that although both the urinary IL-13BP and soluble recombinant IL-13Rα can inhibit the binding of IL-13 to cell surface receptors expressed by macrophages, IL-

13BP is more efficient.

The purification of IL-13BP from mouse urine was shown following SDS-PAGE. The IL-13BP was purified on an IL-13 affinity column and then applied to a RP-HPLC column. The protein was eluted with a gradient of increasing acetonitrile. Each fraction was examined by SDS-PAGE and autoradiography. The results illustrated a silver-stained band with an apparent molecular mass of approximately 45,000 daltons which co-fractionates and is of a similar size to the IL-13BP detected by cross linking.

EXAMPLE 10

CLONING OF MURINE IL-13BP

The partial amino sequence of purified murine IL-13BP is determined. N-terminal, C-terminal and/or internal sequence is generally used. These data are used to generate oligonucleotide probes or primers to clone out the murine IL-13BP. Alternative cloning protocols include screening for murine IL-13BP expression using anti-IL-13BP antibodies. A variety of murine cell lines may be used as a source of IL-13BP DNA.

EXAMPLE 11

CLONING OF HUMAN IL-13BP

Methods similar to those in Example 10 are used to clone the human IL-13BP gene. Alternative methods include cross hybridization using the murine IL-13BP nucleotide sequence. A variety of human cell lines may be used as a source of human IL-13BP DNA.

EXAMPLE 12
N-TERMINAL AMINO ACID SEQUENCE

The IL-13BP isolated according to Example 8 was subjected to N-terminal amino acid sequencing and the sequence is set forth substantially as follows:

EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1].

More particularly the N-terminal sequence is EIKVNPPQDFEIXDPGLLGYLYLQ [SEQ ID NO:13].

Even more particularly the N-terminal sequence is EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21]

EXAMPLE 13
CLONING OF HUMAN IL-13BP

The N-terminal amino acid sequence of murine IL-13BP (Example 12) was used to scan gene/EST databases.

In EST R52795, the region of homology with murine IL-13BP appeared to be C-terminal of an initiation methionine residue which was followed by a putative signal sequence, at the end of which was a canonical von Heijne signal sequence cleavage point. The region of homology, therefore, occurred at the beginning of the mature coding region, consistent with the EST encoding a secreted protein that was the human homologue of the murine IL-13BP. Additionally, the N-terminal amino acid sequence of the mouse IL-13BP shared significant homology with both the murine and human the IL-5 receptor α-chains, members of the haemopoietin receptor family which are known to bind to four-alpha helical cytokines such as IL-13.

The nucleotide sequence of R52795 (see SEQ ID NO:5, encodes N-terminal region of IL-

13BP) was obtained by sequencing the 5' end of a cDNA clone from a human infant brain library. The clone number was YG99F10. The 3' end of this clone was also sequenced. Translation of SEQ ID NO:5 in each of three reading frames is shown in SEQ ID NOs. 6, 7 and 8, respectively. Referring to SEQ ID NO:5, a region identical to murine IL-13BP N-terminal amino acid sequence is the amino acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] which is in SEQ ID NO:6 and begins at nucleotide 211 and ends at nucleotide 282 of SEQ ID NO:5. A possible initiator methione can be seen at nucleotide 127 of SEQ ID NO:5 and a putative signal sequence follows with the amino acid sequence in SEQ ID NO:6 of:

AFVCLAIGCLYTFLISTTFGCTSSS [SEQ ID NO:14].

The putative signal sequence cleaving point would be between S and D at nucleotide positions 202 to 207. The three putative amino acid translations given at SEQ ID NOs:6-8 have been translated from nucleotide 1, 5 and 3 of SEQ ID NO:5, respectively.

These results indicate that the IL-13BP is a member of the haemopoietin receptor family and, moreover, provides a means of cloning the cDNA using oligonucleotides designed from the 5' and 3' ESTs of clone YG99F10. An example of suitable oligonucleotides is 5' ATGGCTTTCGTTTGCTTGGCTATC3' [SEQ ID NO:2] nucl 127-150 of R52795 and 5'CAACATTCGCAAGAAAAATTCAGTTTATT3' [SEQ ID NO:3] nucl 12-40 of R52796. The nucleotide sequence of R52796 is shown in SEQ ID NO:9 (encoding C-terminal region of IL-13BP) and three putative translations in different reading frames are shown in SEQ ID NOs: 10, 11 and 12, respectively. The reading frame showing a WSXWS motif is shown in SEQ ID NO:12 (nucleotides 171-185). The three putative reading frames given in SEQ ID NOs: 10-12 have been translated from nucleotides 1, 2 and 3, respectively of SEQ ID NO:9. The cloning product (eg. PCR product) is cloned into a mammalian expression vector such as pEF-BOS (Mizushima and Nagata, 1990), and the ability of the clone to encode the IL-13BP tested by transfection into COS cells and testing the ability of transfected cells to bind IL-13 with high affinity.

EXAMPLE 14

CLONING OF FULL LENGTH HUMAN IL-13BP

The EST YG99F10 was obtained from ATCC and sequenced in full.

PCR was carried out on the ATCC plasmid using the following primers, with conventional conditions.

FORWARD 5' ATGCGGCGCGCCAGGAGATAAAAGTTAACCCT 3' [SEQ ID NO:15]
REVERSE 5'AGCTACGCGTTCAACGTAGCAAAGTTTTCTTCGATAG3'[SEQ ID NO:16]

The resultant product was digested with Asc I and Mlu I and cloned into the Mlu I site of pEF/FLAG/IL-3SS to yield a cDNA encoding the mouse IL-3 signal sequence, an N-terminal FLAG epitope tag and the mature extracellular domain (EIKVNP..to..KKTLLR) of human IL-13BP. This nucleotide sequence and corresponding amino acid sequence is shown in SEQ ID NO:17. The amino acid sequence alone is shown in SEQ ID NO:18.

With reference to SEQ ID NO:17, the amino acid sequence from residue 1 (Met) to residue 33 (Gln) comprises the initiating methione and signal sequence of murine IL-3. The Flag epitope sequence follows (DYKDDDK-[SEQ ID NO:4]) and then the sequence of the mature IL-13 BP in which transcription has been terminated prior to the transmembrane domain to generate a soluble form.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: THERAPEUTIC MOLECULES

(iii) NUMBER OF SEQUENCES: 22

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Xaa Asp
5 10

Pro Gly Xaa Leu Gly Tyr Leu Tyr Leu Gln
15 20

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGGCTTTCG TTTGCTTGGC TATC 24

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CAACATTCGC AAGAAAAATT CAGTTTATT 29

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Asp Tyr Lys Asp Asp Asp Asp Lys
5

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTAAGAACAC TCTCGTGAGT nCTAACGGTC TTCCGGATGA AGGCTATTTG AAGTCGCCAT 60

AACCTGGTCA GAAGTGTGCC TGTCGGCGGG GAGAGAGGCA ATATCAAGGT TTTAAATCTC 120

GGAGAAATGG CTTTCGTTTG CTTGGCTATC GGATGCTTAT ATACCTTTCT GATAAGCACA 180

ACATTTGGCT GTACTTCATC TTCAGACACC GAGATAAAAG TTAACCCTCC TCAGGATTTT 240

GAGATAGTGG ATCCCGGATA CTTAGGTTAT CTCTATTTGC AATGGCAACC CCCACTGTCT 300

CTGGATCATT TTAAGGAATG CACAGTGGAA TATGAACTAA AATACCGAAA CATTGGTAGT 360

GAAACATGGG AAGGACCATC ATTACTAAGA ATCTACATTT ACAAAGGATG GGGTTTGGAT 420

CnTTAACAAG GGGCATTGAA GGCGAAGGTT ACACACGGTT TTTACCCTGG GGC 473

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 157 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 1-471 of SEQ ID NO:5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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Val Arg Thr Leu Ser  *  Xaa Leu Thr Val Phe Arg Met Lys Ala Ile
 1               5                  10                  15

 *  Ser Arg His Asn Leu Val Arg Ser Val Pro Val Gly Gly Glu Arg
            20                  25                  30

Gly Asn Ile Lys Val Leu Asn Leu Gly Glu Met Ala Phe Val Cys Leu
        35                  40                  45

Ala Ile Gly Cys Leu Tyr Thr Phe Leu Ile Ser Thr Thr Phe Gly Cys
    50                  55                  60

Thr Ser Ser Ser Asp Thr Glu Ile Lys Val Asn Pro Pro Gln Asp Phe
65                  70                  75                  80

Glu Ile Val Asp Pro Gly Tyr Leu Gly Tyr Leu Tyr Leu Gln Trp Gln
                85                  90                  95

Pro Pro Leu Ser Leu Asp His Phe Lys Glu Cys Thr Val Glu Tyr Glu
            100                 105                 110

Leu Lys Tyr Arg Asn Ile Gly Ser Glu Thr Trp Glu Gly Pro Ser Leu
        115                 120                 125

Leu Arg Ile Tyr Ile Tyr Lys Gly Trp Gly Leu Asp Xaa  *  Gln Gly
    130                 135                 140

Ala Leu Lys Ala Lys Val Thr His Gly Phe Tyr Pro Gly
145                 150                 155
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(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 156 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 5-473 of SEQ ID NO:5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

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Glu His Ser Arg Glu Xaa  *  Arg Ser Ser Gly  *  Arg Leu Phe Glu
 1               5                  10                  15

Val Ala Ile Thr Trp Ser Glu Val Cys Leu Ser Ala Gly Arg Glu Ala
            20                  25                  30

Ile Ser Arg Phe  *  Ile Ser Glu Lys Trp Leu Ser Phe Ala Trp Leu
        35                  40                  45
```

```
Ser Asp Ala Tyr Ile Pro Phe  *    *  Ala Gln His Leu Ala Val Leu
     50                  55                  60

His Leu Gln Thr Pro Arg  *  Lys Leu Thr Leu Leu Arg Ile Leu Arg
 65                  70                  75                  80

 *  Trp Ile Pro Asp Thr  *  Val Ile Ser Ile Cys Asn Gly Asn Pro
                85                  90                  95

His Cys Leu Trp Ile Ile Leu Arg Asn Ala Gln Trp Asn Met Asn  *
            100                 105                 110

Asn Thr Glu Thr Leu Val Val Lys His Gly Lys Asp His His Tyr  *
        115                 120                 125

Glu Ser Thr Phe Thr Lys Asp Gly Val Trp Ile Xaa Asn Lys Gly His
    130                 135                 140

 *  Arg Arg Arg Leu His Thr Val Phe Thr Leu Gly
145                 150                 155
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(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 157 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 3-473 of SEQ ID NO:5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

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Lys Asn Thr Leu Val Ser Xaa Asn Gly Leu Pro Asp Glu Gly Tyr Leu
  1               5                  10                  15

Lys Ser Pro  *  Pro Gly Gln Lys Cys Ala Cys Arg Arg Gly Glu Arg
            20                  25                  30

Gln Tyr Gln Gly Phe Lys Ser Arg Arg Asn Gly Phe Arg Leu Leu Gly
        35                  40                  45

Tyr Arg Met Leu Ile Tyr Leu Ser Asp Lys His Asn Ile Trp Leu Tyr
     50                  55                  60

Phe Ile Phe Arg His Arg Asp Lys Ser  *  Pro Ser Ser Gly Phe  *
 65                  70                  75                  80

Asp Ser Gly Ser Arg Ile Leu Arg Leu Ser Leu Phe Ala Met Ala Thr
                85                  90                  95

Pro Thr Val Ser Gly Ser Phe  *  Gly Met His Ser Gly Ile  *  Thr
            100                 105                 110
```

```
Lys Ile Pro Lys His Trp  *   *  Asn Met Gly Arg Thr Ile Ile Thr
        115                 120                 125

Lys Asn Leu His Leu Gln Arg Met Gly Phe Gly Xaa Leu Thr Arg Gly
    130                 135                 140

Ile Glu Gly Glu Gly Tyr Thr Arg Phe Leu Pro Trp Gly
145                 150                 155
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(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 465 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..465

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

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GGTGTTTTGG ATTATGGAAA TTGGnGACCA GAGAAGATGG ATACCTACCT TGGTGACTGC      60

CTACAGTTGA AAATGAAACA TACACCCTTG AAAACAACAA ATGAAACCCG ACAATTATGC     120

CTTTGTAGTA AGAAGCAAAG TGAATATTTA TTGCCTCAGA TGACGGAATT TGGAGTGAGT     180

GGAGTGATAA ACAATGCTGG GAAGGTGAAG ACCTATCGAA GAAAACTTTG CCTACGTTTC     240

TGGCTACCAT TTGGTTTCAT CTTAATATTA GTTATATTTG TAACCGGTCT GCTTTTGCGT     300

AAGCCAAACA CCTACCCAAA AATGATTCCA GAATTTTTCT GTGATACATG AAGACTTTCC     360

ATATCAAGAG ACATGGTATT GACTCAACAG TTTCCAGTCA TGGCCAAATG TTCAAAATAA     420

GTCTCAATAA ACTGAATTTT TCTTGCGAAT GTTGAAAAAA AAAAA                     465
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 155 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 1-465 of SEQ ID NO:9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Gly Val Leu Asp Tyr Gly Asn Trp Xaa Pro Glu Lys Met Asp Thr Tyr
  1               5                  10                  15

Leu Gly Asp Cys Leu Gln Leu Lys Met Lys His Thr Pro Leu Lys Thr
             20                  25                  30

Thr Asn Glu Thr Arg Gln Leu Cys Leu Cys Ser Lys Lys Gln Ser Glu
         35                  40                  45

Tyr Leu Leu Pro Gln Met Thr Glu Phe Gly Val Ser Gly Val Ile Asn
     50                  55                  60

Asn Ala Gly Lys Val Lys Thr Tyr Arg Arg Lys Leu Cys Leu Arg Phe
 65                  70                  75                  80

Trp Leu Pro Phe Gly Phe Ile Leu Ile Leu Val Ile Phe Val Thr Gly
                 85                  90                  95

Leu Leu Leu Arg Lys Pro Asn Thr Tyr Pro Lys Met Ile Pro Glu Phe
            100                 105                 110

Phe Cys Asp Thr  *  Arg Leu Ser Ile Ser Arg Asp Met Val Leu Thr
        115                 120                 125

Gln Gln Phe Pro Val Met Ala Lys Cys Ser Lys  *  Val Ser Ile Asn
    130                 135                 140

 *  Ile Phe Leu Ala Asn Val Glu Lys Lys Lys
145                 150                 155
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 154 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 2-463 of SEQ ID NO:9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Val Phe Trp Ile Met Glu Ile Xaa Asp Gln Arg Arg Trp Ile Pro Thr
  1               5                  10                  15

Leu Val Thr Ala Tyr Ser  *  Lys  *  Asn Ile His Pro  *  Lys Gln
             20                  25                  30

Gln Met Lys Pro Asp Asn Tyr Ala Phe Val Val Arg Ser Lys Val Asn
         35                  40                  45
```

```
Ile Tyr Cys Leu Arg  *  Arg Asn Leu Glu  *  Val Glu  *   *  Thr
     50                 55                  60

Met Leu Gly Arg  *  Arg Pro Ile Glu Glu Asn Phe Ala Tyr Val Ser
 65                 70                  75                  80

Gly Tyr His Leu Val Ser Ser  *  Tyr  *  Leu Tyr Leu  *  Pro Val
                85                  90                  95

Cys Phe Cys Val Ser Gln Thr Pro Thr Gln Lys  *  Phe Gln Asn Phe
            100                 105                 110

Ser Val Ile His Glu Asp Phe Pro Tyr Gln Glu Thr Trp Tyr  *  Leu
        115                 120                 125

Asn Ser Phe Gln Ser Trp Pro Asn Val Gln Asn Lys Ser Gln  *  Thr
    130                 135                 140

Glu Phe Phe Leu Arg Met Leu Lys Lys Lys
145                 150
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 154 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 3-464 of SEQ ID NO:9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Cys Phe Gly Leu Trp Lys Leu Xaa Thr Arg Glu Asp Gly Tyr Leu Pro
  1               5                  10                  15

Trp  *  Leu Pro Thr Val Glu Asn Glu Thr Tyr Thr Leu Glu Asn Asn
            20                  25                  30

Lys  *  Asn Pro Thr Ile Met Pro Leu  *   *  Glu Ala Lys  *  Ile
        35                  40                  45

Phe Ile Ala Ser Asp Asp Gly Ile Trp Ser Glu Trp Ser Asp Lys Gln
     50                  55                  60

Cys Trp Glu Gly Glu Asp Leu Ser Lys Lys Thr Leu Pro Thr Phe Leu
 65                  70                  75                  80

Ala Thr Ile Trp Phe His Leu Asn Ile Ser Tyr Ile Cys Asn Arg Ser
                85                  90                  95

Ala Phe Ala  *  Ala Lys His Leu Pro Lys Asn Asp Ser Arg Ile Phe
            100                 105                 110
```

```
Leu  *  Tyr Met Lys Thr Phe His Ile Lys Arg His Gly Ile Asp Ser
        115                 120                 125

Thr Val Ser Ser His Gly Gln Met Phe Lys Ile Ser Leu Asn Lys Leu
    130                 135                 140

Asn Phe Ser Cys Glu Cys  *  Lys Lys Lys
145                 150
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Xaa Asp Pro Gly Leu Leu Gly
                  5                  10                  15

Tyr Leu Tyr Leu Gln
 20
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Ala Phe Val Cys Lys Ala Ile Gly Cys Leu Tyr Thr Phe Leu Ile Ser Thr Thr Phe
                  5                  10                  15
Gly Cys Thr Ser Ser Ser
 20                  25
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATGCGGCGCG CCAGGAGATA AAAGTTAACC CT 32

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

AGCTACGCGT TCAACGTAGC AAAGTTTTCT TCGATAG 37

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1080 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1080

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ATG GTT CTT GCC AGC TCT ACC ACC AGC ATC CAC ACC ATG CTG CTC CTG        48
Met Val Leu Ala Ser Ser Thr Thr Ser Ile His Thr Met Leu Leu Leu
  1               5                  10                  15

CTC CTG ATG CTC TTC CAC CTG GGA CTC CAA GCT TCA ATC TCG GCG CGC        96
Leu Leu Met Leu Phe His Leu Gly Leu Gln Ala Ser Ile Ser Ala Arg
             20                  25                  30

CAG GAC TAC AAG GAC GAC GAT GAC AAG ACG CGC CAG GAG ATA AAA GTT       144
Gln Asp Tyr Lys Asp Asp Asp Asp Lys Thr Arg Gln Glu Ile Lys Val
         35                  40                  45

AAC CCT CCT CAG GAT TTT GAG ATA GTG GAT CCC GGA TAC TTA GGT TAT       192
```

```
Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly Tyr Leu Gly Tyr
     50                  55                  60

CTC TAT TTG CAA TGG CAA CCC CCA CTG TCT CTG GAT CAT TTT AAG GAA      240
Leu Tyr Leu Gln Trp Gln Pro Pro Leu Ser Leu Asp His Phe Lys Glu
 65                  70                  75                  80

TGC ACA GTG GAA TAT GAA CTA AAA TAC CGA AAC ATT GGT AGT GAA ACA      288
Cys Thr Val Glu Tyr Glu Leu Lys Tyr Arg Asn Ile Gly Ser Glu Thr
                 85                  90                  95

TGG AAG ACC ATC ATT ACT AAG AAT CTA CAT TAC AAA GAT GGG TTT GAT      336
Trp Lys Thr Ile Ile Thr Lys Asn Leu His Tyr Lys Asp Gly Phe Asp
            100                 105                 110

CTT AAC AAG GGC ATT GAA GCG AAG ATA CAC ACG CTT TTA CCA TGG CAA      384
Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu Leu Pro Trp Gln
        115                 120                 125

TGC ACA AAT GGA TCA GAA GTT CAA AGT TCC TGG GCA GAA ACT ACT TAT      432
Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala Glu Thr Thr Tyr
    130                 135                 140

TGG ATA TCA CCA CAA GGA ATT CCA GAA ACT AAA GTT CAG GAT ATG GAT      480
Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val Gln Asp Met Asp
145                 150                 155                 160

TGC GTA TAT TAC AAT TGG CAA TAT TTA CTC TGT TCT TGG AAA CCT GGC      528
Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser Trp Lys Pro Gly
                165                 170                 175

ATA GGT GTA CTT CTT GAT ACC AAT TAC AAC TTG TTT TAC TGG TAT GAG      576
Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe Tyr Trp Tyr Glu
            180                 185                 190

GGC TTG GAT CAT GCA TTA CAG TGT GTT GAT TAC ATC AAG GCT GAT GGA      624
Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile Lys Ala Asp Gly
        195                 200                 205

CAA AAT ATA GGA TGC AGA TTT CCC TAT TTG GAG GCA TCA GAC TAT AAA      672
Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala Ser Asp Tyr Lys
    210                 215                 220

GAT TTC TAT ATT TGT GTT AAT GGA TCA TCA GAG AAC AAG CCT ATC AGA      720
Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn Lys Pro Ile Arg
225                 230                 235                 240

TCC AGT TAT TTC ACT TTT CAG CTT CAA AAT ATA GTT AAA CCT TTG CCG      768
Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val Lys Pro Leu Pro
                245                 250                 255

CCA GTC TAT CTT ACT TTT ACT CGG GAG AGT TCA TGT GAA ATT AAG CTG      816
Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys Glu Ile Lys Leu
            260                 265                 270

AAA TGG AGC ATA CCT TTG GGA CCT ATT CCA GCA AGG TGT TTT GAT TAT      864
```

```
Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg Cys Phe Asp Tyr
        275                 280                 285

GAA ATT GAG ATC AGA GAA GAT GAT ACT ACC TTG GTG ACT GCT ACA GTT      912
Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val Thr Ala Thr Val
    290                 295                 300

GAA AAT GAA ACA TAC ACC TTG AAA ACA ACA AAT GAA ACC CGA CAA TTA      960
Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu Thr Arg Gln Leu
305                 310                 315                 320

TGC TTT GTA GTA AGA AGC AAA GTG AAT ATT TAT TGC TCA GAT GAC GGA     1008
Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys Ser Asp Asp Gly
                325                 330                 335

ATT TGG AGT GAG TGG AGT GAT AAA CAA TGC TGG GAA GGT GAA GAC CTA     1056
Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu Gly Glu Asp Leu
            340                 345                 350

TCG AAG AAA ACT TTG CTA CGT TG                                     1080
Ser Lys Lys Thr Leu Leu Arg
        355                 360
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 359 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Met Val Leu Ala Ser Ser Thr Thr Ser Ile His Thr Met Leu Leu Leu
  1               5                  10                  15

Leu Leu Met Leu Phe His Leu Gly Leu Gln Ala Ser Ile Ser Ala Arg
            20                  25                  30

Gln Asp Tyr Lys Asp Asp Asp Asp Lys Thr Arg Gln Glu Ile Lys Val
        35                  40                  45

Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly Tyr Leu Gly Tyr
    50                  55                  60

Leu Tyr Leu Gln Trp Gln Pro Pro Leu Ser Leu Asp His Phe Lys Glu
65                  70                  75                  80

Cys Thr Val Glu Tyr Glu Leu Lys Tyr Arg Asn Ile Gly Ser Glu Thr
                85                  90                  95

Trp Lys Thr Ile Ile Thr Lys Asn Leu His Tyr Lys Asp Gly Phe Asp
            100                 105                 110
```

```
Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu Leu Pro Trp Gln
        115                 120                 125

Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala Glu Thr Thr Tyr
    130                 135                 140

Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val Gln Asp Met Asp
145                 150                 155                 160

Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser Trp Lys Pro Gly
                165                 170                 175

Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe Tyr Trp Tyr Glu
            180                 185                 190

Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile Lys Ala Asp Gly
        195                 200                 205

Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala Ser Asp Tyr Lys
    210                 215                 220

Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn Lys Pro Ile Arg
225                 230                 235                 240

Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val Lys Pro Leu Pro
                245                 250                 255

Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys Glu Ile Lys Leu
            260                 265                 270

Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg Cys Phe Asp Tyr
        275                 280                 285

Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val Thr Ala Thr Val
    290                 295                 300

Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu Thr Arg Gln Leu
305                 310                 315                 320

Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys Ser Asp Asp Gly
                325                 330                 335

Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu Gly Glu Asp Leu
            340                 345                 350

Ser Lys Lys Thr Leu Leu Arg
        355
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 948 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..948

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
GAG ATA AAA GTT AAC CCT CCT CAG GAT TTT GAG ATA GTG GAT CCC GGA          48
Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly
  1               5                  10                  15

TAC TTA GGT TAT CTC TAT TTG CAA TGG CAA CCC CCA CTG TCT CTG GAT          96
Tyr Leu Gly Tyr Leu Tyr Leu Gln Trp Gln Pro Pro Leu Ser Leu Asp
            20                  25                  30

CAT TTT AAG GAA TGC ACA GTG GAA TAT GAA CTA AAA TAC CGA AAC ATT         144
His Phe Lys Glu Cys Thr Val Glu Tyr Glu Leu Lys Tyr Arg Asn Ile
        35                  40                  45

GGT AGT GAA ACA TGG AAG ACC ATC ATT ACT AAG AAT CTA CAT TAC AAA         192
Gly Ser Glu Thr Trp Lys Thr Ile Ile Thr Lys Asn Leu His Tyr Lys
    50                  55                  60

GAT GGG TTT GAT CTT AAC AAG GGC ATT GAA GCG AAG ATA CAC ACG CTT         240
Asp Gly Phe Asp Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu
65                  70                  75                  80

TTA CCA TGG CAA TGC ACA AAT GGA TCA GAA GTT CAA AGT TCC TGG GCA         288
Leu Pro Trp Gln Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala
                85                  90                  95

GAA ACT ACT TAT TGG ATA TCA CCA CAA GGA ATT CCA GAA ACT AAA GTT         336
Glu Thr Thr Tyr Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val
            100                 105                 110

CAG GAT ATG GAT TGC GTA TAT TAC AAT TGG CAA TAT TTA CTC TGT TCT         384
Gln Asp Met Asp Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser
        115                 120                 125

TGG AAA CCT GGC ATA GGT GTA CTT CTT GAT ACC AAT TAC AAC TTG TTT         432
Trp Lys Pro Gly Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe
    130                 135                 140

TAC TGG TAT GAG GGC TTG GAT CAT GCA TTA CAG TGT GTT GAT TAC ATC         480
Tyr Trp Tyr Glu Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile
145                 150                 155                 160

AAG GCT GAT GGA CAA AAT ATA GGA TGC AGA TTT CCC TAT TTG GAG GCA         528
Lys Ala Asp Gly Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala
                165                 170                 175

TCA GAC TAT AAA GAT TTC TAT ATT TGT GTT AAT GGA TCA TCA GAG AAC         576
Ser Asp Tyr Lys Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn
```

```
            180                 185                 190

AAG CCT ATC AGA TCC AGT TAT TTC ACT TTT CAG CTT CAA AAT ATA GTT      624
Lys Pro Ile Arg Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val
        195                 200                 205

AAA CCT TTG CCG CCA GTC TAT CTT ACT TTT ACT CGG GAG AGT TCA TGT      672
Lys Pro Leu Pro Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys
    210                 215                 220

GAA ATT AAG CTG AAA TGG AGC ATA CCT TTG GGA CCT ATT CCA GCA AGG      720
Glu Ile Lys Leu Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg
225                 230                 235                 240

TGT TTT GAT TAT GAA ATT GAG ATC AGA GAA GAT GAT ACT ACC TTG GTG      768
Cys Phe Asp Tyr Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val
                245                 250                 255

ACT GCT ACA GTT GAA AAT GAA ACA TAC ACC TTG AAA ACA ACA AAT GAA      816
Thr Ala Thr Val Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu
            260                 265                 270

ACC CGA CAA TTA TGC TTT GTA GTA AGA AGC AAA GTG AAT ATT TAT TGC      864
Thr Arg Gln Leu Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys
        275                 280                 285

TCA GAT GAC GGA ATT TGG AGT GAG TGG AGT GAT AAA CAA TGC TGG GAA      912
Ser Asp Asp Gly Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu
    290                 295                 300

GGT GAA GAC CTA TCG AAG AAA ACT TTG CTA CGT TG                      948
Gly Glu Asp Leu Ser Lys Lys Thr Leu Leu Arg
305                 310                 315
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 315 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly
  1               5                  10                  15

Tyr Leu Gly Tyr Leu Tyr Leu Gln Trp Gln Pro Pro Leu Ser Leu Asp
            20                  25                  30

His Phe Lys Glu Cys Thr Val Glu Tyr Glu Leu Lys Tyr Arg Asn Ile
        35                  40                  45

Gly Ser Glu Thr Trp Lys Thr Ile Ile Thr Lys Asn Leu His Tyr Lys
```

```
     50                  55                  60

Asp Gly Phe Asp Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu
 65                  70                  75                  80

Leu Pro Trp Gln Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala
                 85                  90                  95

Glu Thr Thr Tyr Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val
            100                 105                 110

Gln Asp Met Asp Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser
        115                 120                 125

Trp Lys Pro Gly Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe
    130                 135                 140

Tyr Trp Tyr Glu Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile
145                 150                 155                 160

Lys Ala Asp Gly Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala
                165                 170                 175

Ser Asp Tyr Lys Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn
            180                 185                 190

Lys Pro Ile Arg Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val
        195                 200                 205

Lys Pro Leu Pro Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys
    210                 215                 220

Glu Ile Lys Leu Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg
225                 230                 235                 240

Cys Phe Asp Tyr Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val
                245                 250                 255

Thr Ala Thr Val Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu
            260                 265                 270

Thr Arg Gln Leu Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys
        275                 280                 285

Ser Asp Asp Gly Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu
    290                 295                 300

Gly Glu Asp Leu Ser Lys Lys Thr Leu Leu Arg
305                 310                 315
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Leu Asp Pro Gly Leu Leu Gly
5 10 15

Tyr Leu Tyr Leu Gln
20

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly Tyr Leu Gly
5 10 15

Tyr Leu Tyr Leu Gln
20

CLAIMS:

1. An isolated proteinaceous molecule or a recombinant or synthetic form thereof capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13Rα.

2. An isolated proteinaceous molecule according to claim 1 having a molecular weight in its native soluble form as determined by SDS-PAGE of from about 40,000 daltons to about 60,000 daltons.

3. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.

4. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.

5. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.

6. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

7. An isolated proteinaceous molecule according to claim 2 or 3 or 4 or 5 comprising an N-terminal amino acid sequence set forth in one of SEQ ID NO:6 or 7 or 8.

8. An isolated proteinaceous molecule according to claim 2 or 3 or 4 or 5 comprising a C-terminal amino acid sequence set forth in one of SEQ ID NO:10 or 11 or 12.

9. An isolated proteinaceous molecule according to claim 6 comprising an amino acid sequence set forth in SEQ ID NO:20.

10. An isolated proteinaceous molecule according to any one of claims 2 to 6 encoded by a nucleotide sequence substantially as set forth in SEQ ID NO:5 or SEQ ID NO:9 or SEQ ID NO:19 or a nucleotide sequence having at least about 50% similarity thereto and which is capable of hybridising thereto under low stringency conditions at 42°C.

11. An isolated nucleic acid molecule comprising a sequence of nucleotides which encodes or is complementary to a sequence which encodes a proteinaceous molecule capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13Rα.

12. An isolated nucleic acid molecule according to claim 11 wherein said encoded proteinaceous molecule in its native form has a molecular weight of from about 40,000 daltons to about 60,000 daltons as determined by SDS-PAGE.

13. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.

14. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.

15. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.

16. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

17. An isolated nucleic acid molecule according to claim 13 or 14 or 15 or 16 encoding an N-terminal amino acid sequence set forth in at least one of SEQ ID NO:6 or 7 or 8 or an amino acid sequence having at least 50% similarity to one of SEQ ID NO:6 or 7 or 8.

18. An isolated nucleic acid molecule according to claim 13 or 14 or 15 or 16 encoding a C-terminal amino acid sequence as set forth in at least one of SEQ ID NO:10 or 11 or 12.

19. An isolated nucleic acid molecule according to claim 16 encoding an amino acid sequence as set forth in SEQ ID NO:20.

20. An isolated nucleic acid molecule according to claim 11 comprising a nucleotide sequence substantially as set forth in SEQ ID NO:5 or 9 or 19 or a nucleotide sequence having at least about 50% similarity thereto and which is capable of hybridising thereto under low stringency conditions at 42°C.

21. An expression vector comprising a promoter operably linked to a nucleic acid molecule as defined in any one of claims 11 to 20.

22. A method for purifying IL-13BP or its derivatives from a biological sample including body fluid or cell culture medium, said method comprising contacting said biological sample with immobilised IL-13 or an IL-13/IL-4 hybrid or a binding derivative thereof for a time and under conditions sufficient for a complex to form between said IL-3 and its binding protein, eluting said IL-13BP or IL-13/IL-4 from the immobilised IL-13 and collecting said eluted IL-13BP or IL-13/IL-4.

23. A peptide having first and second portions wherein one of said first and second portions is IL-13BP or a functional derivative thereof and the other of said first and second portions is IL-4BP or a functional derivative thereof wherein said polypeptide is capable of modulating biological processes involving IL-13 and/or IL-4.

24. A polypeptide according to claim 23 comprising the amino acid sequence

EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.

25. A polypeptide according to claim 23 comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.

26. A polypeptide according to claim 23 comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.

27. A polypeptide according to claim 23 comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

28. A polypeptide according to claim 23 comprising an amino acid sequence of one of SEQ ID NO:6 or 7 or 8.

29. A polypeptide according to claim 23 comprising an amino acid sequence of one of SEQ ID NO:10 or 11 or 12.

30. A polypeptide according to claim 23 comprising the amino acid sequence set forth in SEQ ID NO:20.

31. A method of treatment comprising administering to a patient an IL-13 antagonising effective amount of an IL-13BP or its derivative for a time and under conditions sufficient to antagonise at least one property of IL-13.

32. A method according to claim 31 wherein the treatment is for an allergic reaction.

33. A composition comprising a proteinaceous molecule according to any one of claims

1 to 10 and one or more pharmaceutically acceptable carriers and/or diluents.

34. An antibody to a proteinaceous molecule according to any one of claims 1 to 10.

35. An antibody according to claim 34 wherein the antibody is a monoclonal antibody.

36. A transgenic animal comprising a mutation in at least one allele of the gene encoding IL-13BP.

37. A transgenic animal according to claim 36 comprising a mutation in two alleles of the gene encoding IL-13BP.

38. A transgenic animal according to claim 36 or 37 wherein said animal is a murine animal.

FIGURE 1

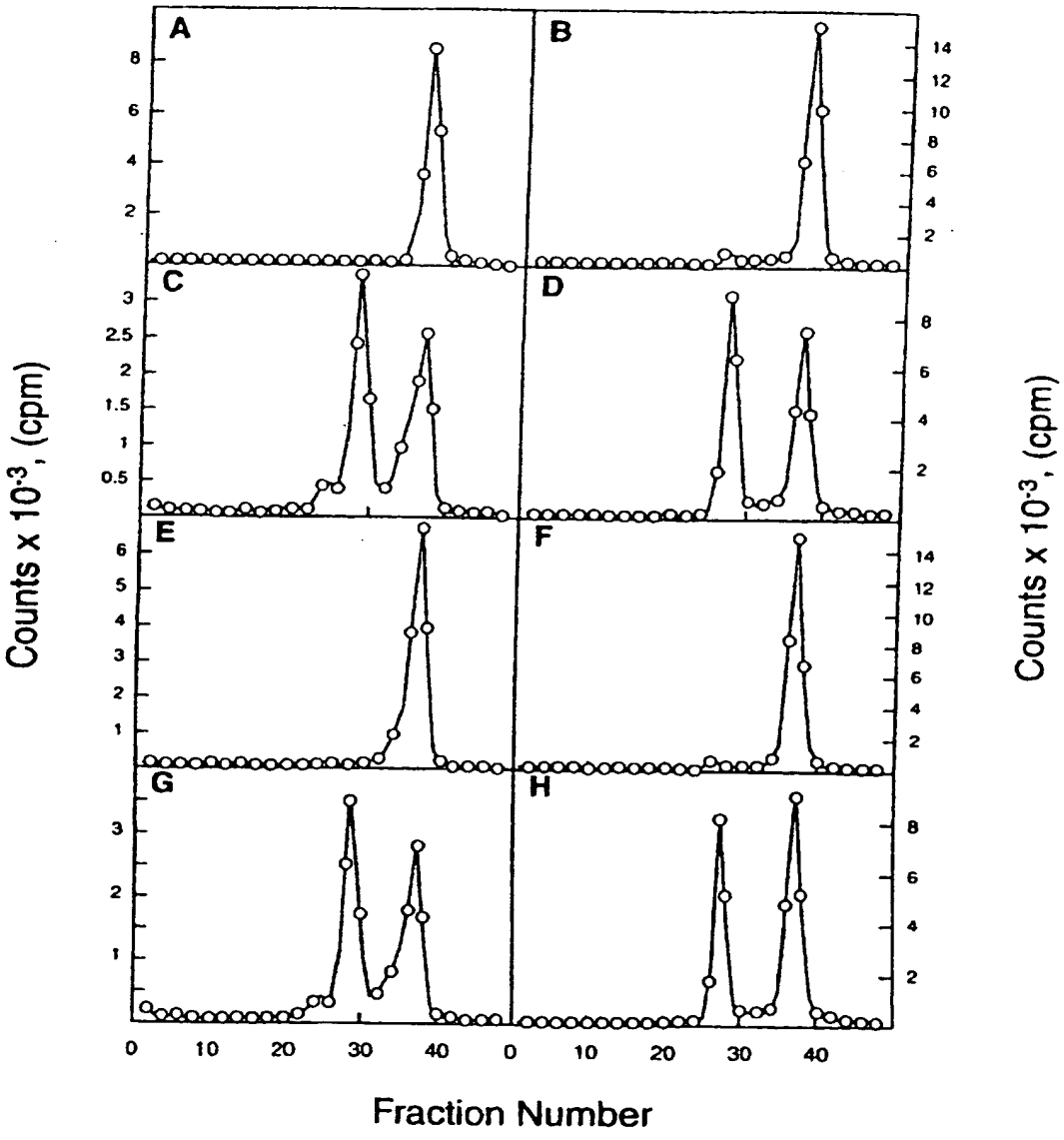

A
B
C
D
E
F
G
H
Counts x 10-3, (cpm)
Counts x 10-3, (cpm)
0 10 20 30 40 0 10 20 30 40
Fraction Number

FIGURE 2

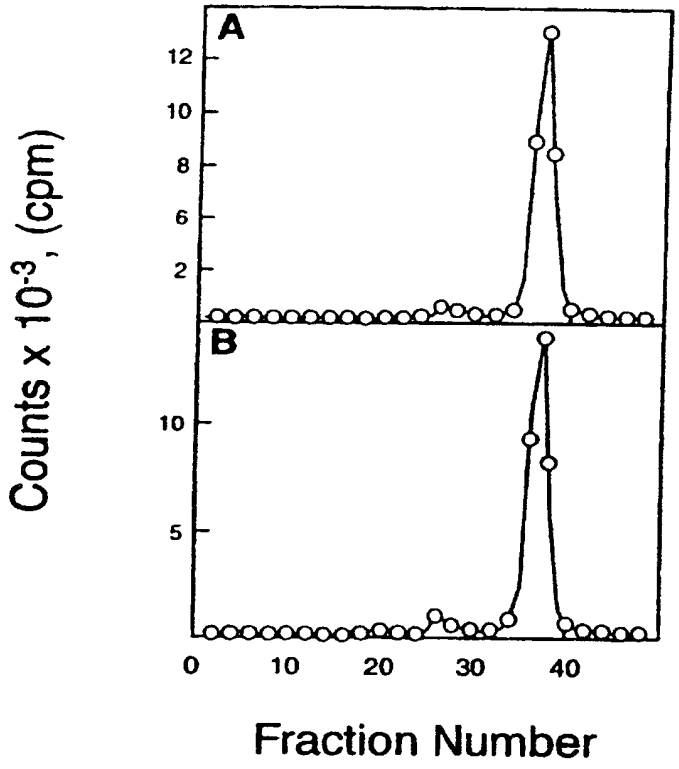
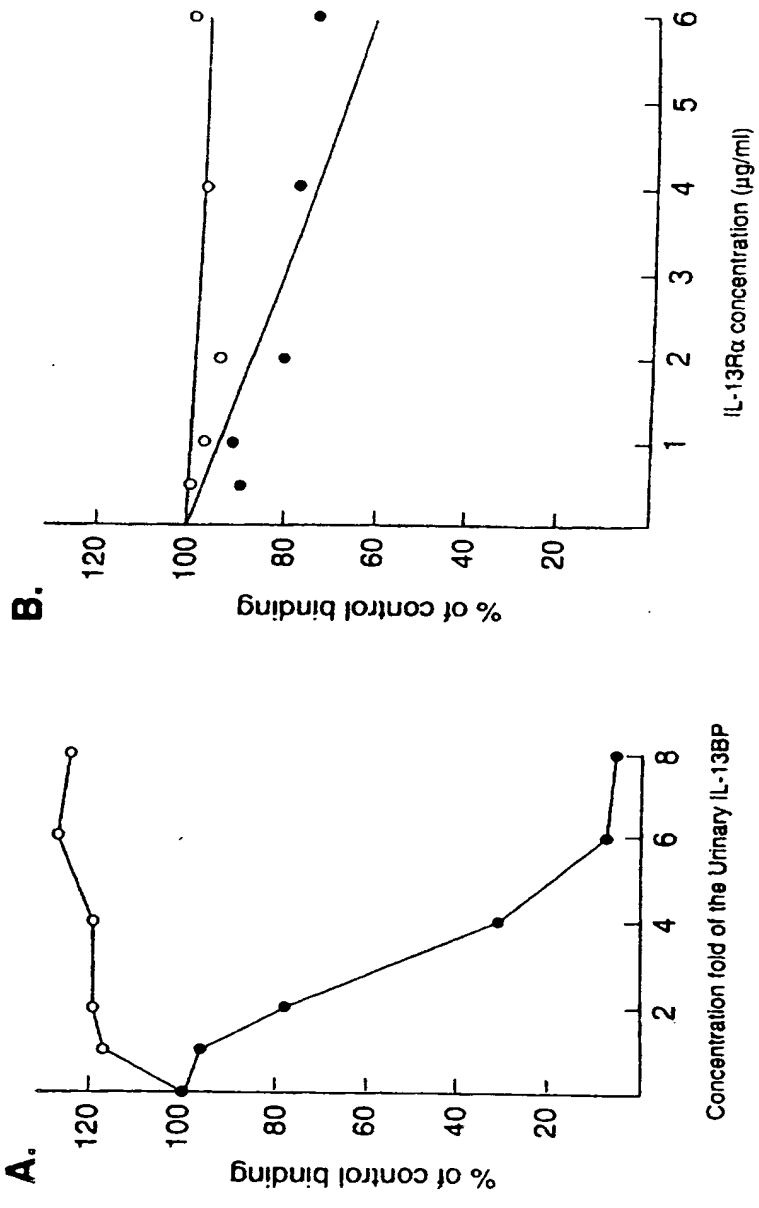


FIGURE 3


B.
% of control binding
120
100
80
60
40
20
1
2
3
4
5
6
IL-13Rα concentration (µg/ml)
A.
% of control binding
120
100
80
60
40
20
2
4
6
8
Concentration fold of the Urinary IL-13BP

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU97/00591

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A01K 67/00, 67/027, A61K 38/17, C07K 14/47, 16/18, C12N 15/12, 15/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
WPAT Derwent Database; Chemical Abstracts - Keywords below

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Medline - Keywords below, EMBL, GENEBANK, SWISS Prot, PIR

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT, Chemical Abstracts, Medline - Keywords: IL, interleukin, 13, 13BP:, 13R:, 4, 4BP:, 4R:, bind:, antag:, antibod:, recept:
EMBL, GENEBANK, SWISS Prot, PIR - Sequence Search: SEQ ID NOS 1, 7, 8, 10, 12, 13, 21, 22

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Immunology, volume 87, number 4, 1996, Bost et al., "In vivo treatment with anti-interleukin-13 antibodies significantly reduces the humoral immune response against an oral immunogen in mice", pages 633-641.	1, 2, 31
X	WO, 94/04680(Schering Corporation) 3 March 1994	1, 2, 31
P,X	WO, 97/20926(SANOFI) 12 June 1997	1-22, 31-35

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
29 October 1997

Date of mailing of the international search report
30 OCT 1997

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU97/00591

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	European Journal of Immunology, volume 27, number 4, 1997, Gauchat et al., "A novel 4-kb interleukin-13 receptor α mRNA expressed in human B, T, and endothelial cells encoding an alternate type-II interleukin-4/interleukin-13 receptor", pages 971-978.	1-22, 31-35
P,X	The Journal of Biological Chemistry, volume 272, number 14, 1997, Zhang et al., "Identification, Purification, and Characterization of a Soluble Interleukin (IL)-13-binding Protein", pages 9474-9480.	1-22, 31-35

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/AU97/00591

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO	94/04680	JP	7508179
		US	5596072
		EP	656947
WO	97/20926	AU	75760/96
		FR	2742156

END OF ANNEX